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Randomized Comparison of Prasugrel (CS-747, LY640315), a Novel Thienopyridine $P2Y_{12}$ Antagonist, With Clopidogrel in Percutaneous Coronary Intervention

Results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)–TIMI 26 Trial

Stephen D. Wiviott, MD; Elliott M. Antman, MD; Kenneth J. Winters, MD; Govinda Weerakkody, PhD; Sabina A. Murphy, MS; Bruce D. Behounek, MD; Robert J. Carney, MD; Charles Lazzam, MD; Raymond G. McKay, MD; Carolyn H. McCabe, BS; Eugene Braunwald, MD; for the JUMBO–TIMI 26 Investigators

Background—Despite the current standard antiplatelet regimen of aspirin and clopidogrel (with or without glycoprotein IIb/IIIa inhibitors) in percutaneous coronary intervention patients, periprocedural and postprocedural ischemic events continue to occur. Prasugrel (CS-747, LY640315), a novel potent thienopyridine $P2Y_{12}$ receptor antagonist, has the potential to achieve higher levels of inhibition of ADP-induced platelet aggregation than currently approved doses of clopidogrel.

Methods and Results—Joint Utilization of Medications to Block Platelets Optimally–Thrombolysis In Myocardial Infarction 26 (JUMBO-TIMI 26) was a phase 2, randomized, dose-ranging, double-blind safety trial of prasugrel versus clopidogrel in 904 patients undergoing elective or urgent percutaneous coronary intervention. Patients were randomized to either standard dosing with clopidogrel or 1 of 3 prasugrel regimens. Subjects were monitored for 30 days for bleeding and clinical events. The primary end point of the trial was clinically significant (TIMI major plus minor) non–CABG-related bleeding events in prasugrel- versus clopidogrel-treated patients. Hemorrhagic complications were infrequent, with no significant difference between patients treated with prasugrel or clopidogrel in the rate of significant bleeding (1.7% versus 1.2%; hazard ratio, 1.42; 95% CI, 0.40, 5.08). In prasugrel-treated patients, there were numerically lower incidences of the primary efficacy composite end point (30-day major adverse cardiac events) and of the secondary end points myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis.

Conclusions—In this phase 2 study, which was designed to assess safety when administered at the time of percutaneous coronary intervention, prasugrel and clopidogrel both resulted in low rates of bleeding. The results of this trial serve as a foundation for the large phase 3 clinical trial designed to assess both efficacy and safety. (***Circulation*. 2005;111:3366-3373.)**

Key Words: coronary disease ■ drugs ■ hemorrhage ■ platelets ■ stents

Platelet activation and aggregation play important roles in the pathogenesis of cardiac ischemic events after either spontaneous plaque disruption in acute coronary syndromes or mechanical disruption of coronary artery plaques caused by percutaneous coronary intervention (PCI).[1] The use of coronary stents has resulted in a reduced need for recurrent target vessel revascularization but an increased risk of acute and subacute thrombosis[2] of the instrumented vessel. Standard therapy for the prevention of thrombotic events after coronary stenting involves dual antiplatelet therapy with aspirin plus a thienopyridine.[3,4] Thienopyridines block platelet activation and aggregation by inhibiting the $P2Y_{12}$ ADP receptor.[5] Most clinical trials supporting the use of thienopyridines plus aspirin in PCI compared with aspirin alone were conducted with ticlopidine.[6–9] However, clopidogrel has largely replaced ticlopidine for use in PCI because of better

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tolerability and a lower risk of hematologic abnormalities compared with ticlopidine.[10,11]

Despite the widespread use of clopidogrel in patients undergoing PCI with currently available thienopyridines, several important issues remain.[12–15] Data from the Clopidogrel to Reduce Events During Observation (CREDO) trial suggest that most of the acute effect seen in reducing periprocedural events with clopidogrel was limited to patients who received the drug at least 6 hours, and perhaps as many as 15 hours, before the procedure.[16,17] As irreversible inhibitors of platelet function, the effects of thienopyridines are long-lasting, resulting in a reluctance in current clinical practice to give these agents before determining whether a patient is likely to need coronary bypass surgery.[3,18] When bypass surgery is performed within 5 days of treatment with clopidogrel, a significant increase in major bleeding events has been observed.[19] Finally, a significant variability in the response to clopidogrel among healthy subjects and patients undergoing PCI has been observed, with some individuals having minimal inhibition of ADP-induced platelet aggregation.[15,20–22] This concept of clopidogrel resistance led to the concern that some patients may not be adequately protected from the intense platelet activation and aggregation that occur with PCI and are therefore at increased risk for thrombotic events.[14,15,23] Because of these issues, an improved antiplatelet regimen to support PCI is desirable.

Prasugrel (CS-747, LY640315) is a novel thienopyridine antiplatelet agent that has been shown in preclinical studies to be more potent and to have a more rapid onset of action than clopidogrel.[24] Phase 1 studies in healthy human subjects not taking aspirin showed inhibition of platelet aggregation to be greater with a single 60-mg dose of prasugrel than a single 300-mg dose of clopidogrel[25] and that repeated dosing with 10 mg prasugrel showed higher inhibition of platelet aggregation than 75 mg clopdogrel.[26] Furthermore, there is evidence in healthy volunteers that thienopyridine resistance may be less frequent with a loading dose of 60 mg prasugrel than with 300 mg clopidogrel.[25] These features stimulated interest in the evaluation of prasugrel for the prevention of thrombotic events after PCI. In preparation for a future phase 3 trial designed to assess efficacy, the present study is a phase 2, dose-ranging safety trial comparing prasugrel with clopidogrel in patients undergoing PCI. The primary hypothesis for the present study was that prasugrel is as safe as clopidogrel with respect to bleeding events after PCI.

Methods

The study was conducted between April and December 2003 at 80 sites in the United States and Canada (see Appendix in the online-only Data Supplement). The protocol was approved by all relevant local institutional review boards and ethics committees, and all patients signed written informed consent forms before participation.

Study Population

To be eligible for inclusion in the trial, a patient had to (1) be a man or nonpregnant woman ≥18 and ≤75 years of age, (2) be a candidate for elective or urgent PCI with intended coronary stenting, and (3) have a native target coronary artery stenosis >60% (by visual estimation) that was thought by the operator to be amenable to stenting with ≤2 approved coronary stents per lesion (multilesion or multivessel stenting was acceptable if all lesions were treated in a single nonstaged procedure). Patients could have been enrolled before diagnostic catheterization but were randomized only if they subsequently met angiographic eligibility criteria.

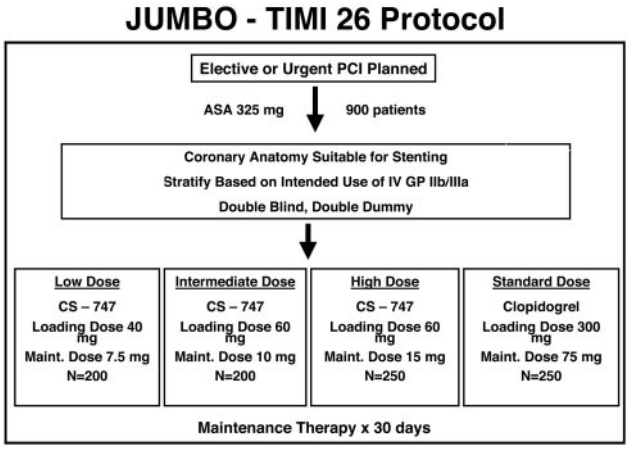

Figure 1. Protocol schema for JUMBO–TIMI 26.

Patients were excluded from the study if any of the following were present: (1) planned PCI procedure as initial treatment for an ST-elevation myocardial infarction (STEMI) or within 24 hours of fibrinolytic therapy for STEMI; (2) left main stenosis ≥50% not protected by at least 1 patent bypass graft; (3) target lesion in a saphenous vein graft or arterial conduit graft; (4) left ventricular ejection fraction <30% by any imaging technique or New York Heart Association (NYHA) class III or IV congestive heart failure or cardiogenic shock; (5) bleeding risks, including, but not limited to, active internal bleeding, history of bleeding diathesis, recent major surgery, or significant trauma; (6) stroke within 2 years, intracranial neoplasm, AV malformation, or aneurysm; (7) uncontrolled hypertension; (8) concomitant therapies, including oral anticoagulation therapy, treatment with a thienopyridine (ticlopidine or clopidogrel) within 5 days, subcutaneous low-molecular-weight heparin within 8 hours before PCI, bivalirudin during the index admission before PCI, a proton pump inhibitor within 12 hours before PCI or in patients scheduled to receive a proton pump inhibitor after PCI (to minimize any potential inhibition of absorption of study medications), oral or intravenous H2 antagonist within 2 hours before PCI, or any investigational drug or device within the previous 30 days.

Study Protocol

JUMBO–TIMI 26 was a multicenter, randomized, parallel-group, double-blind, double-dummy, active-comparator-controlled trial (Figure 1). After diagnostic catheterization, subjects were randomized to either prasugrel or clopidogrel if the angiographic inclusion criteria were met. The study plan was for a total of 900 subjects to be randomized to low-dose (40-mg loading dose followed by 7.5 mg daily), intermediate-dose (60-mg loading dose followed by 10 mg daily), or high-dose (60-mg loading dose followed by 15 mg daily) prasugrel or the standard dose of clopidogrel (300-mg loading dose followed by 75 mg daily) at a 4:4:5:5 ratio (200, 200, 250, 250 subjects). A 300-mg loading dose was chosen for the comparator as the standard dose of clopidogrel in clinical practice. Randomization was stratified on the basis of the investigator's intention to use a glycoprotein (GP) IIb/IIIa inhibitor during PCI. For the purpose of blinding, clopidogrel/placebo was overencapsulated without excipients. Before this study, testing determined that overencapsulated clopidogrel was bioequivalent pharmacokinetically to unencapsulated clopidogrel (according to Food and Drug Administration standards). Study doses of prasugrel were determined from prior pharmacokinetic and pharmacodynamic data.[24,26] Blinded study drug (active prasugrel or clopidogrel and matching placebo) was administered from any time after the completion of the diagnostic angiogram to the time the patient left the recovery room after PCI. After the procedure, a complete blood count was measured daily, and

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creatine kinase-MB (CK-MB) was measured 4 to 8 hours and 12 to 24 hours after the procedure and with any ischemic symptoms. Maintenance therapy was continued for 29 to 34 days. A 30-day visit (range, 29 to 35 days) was held to assess for end points and compliance. Clinical end points were determined at hospital discharge and at the 30-day visit.

Concomitant Medications

All subjects received daily oral treatment with enteric-coated 325 mg aspirin for the duration of the study. The use of GP IIb/IIIa inhibitors was at the discretion of the treating physician. All subjects received unfractionated heparin therapy with target activated clotting times of 200 to 250 seconds for patients receiving an intravenous GP IIb/IIIa inhibitor and 250 to 300 seconds for those not receiving a GP IIb/IIIa inhibitor. At the completion of the study, decisions about continuation and dosing of antiplatelet agents were left to the discretion of the treating physician.

Trial End Points

The primary end point of the trial was non–CABG-related "significant hemorrhage" at 30 days, defined as the composite of TIMI major and minor hemorrhage. Hemorrhagic events were classified as major or minor by use of standard TIMI definitions[27]: a clinically overt (including imaging) hemorrhage with a hemoglobin drop >5 g/dL was considered major, and a clinically overt hemorrhage with a hemoglobin drop of 3 to ≤5 g/dL was considered minor. A clinically overt bleeding episode with <3 g/dL drop in hemoglobin was considered minimal.[28] Additional safety and efficacy end points included major adverse cardiac event (MACE) components individually and in combination. MACE were defined as any one of the following, occurring through the 30-day visit after PCI: (1) death (all-cause mortality), (2) myocardial infarction (MI), (3) stroke, (4) recurrent myocardial ischemia requiring hospitalization, and (5) clinical target vessel thrombosis (CTVT) defined either as total or subtotal occlusion of the target vessel documented angiographically and occurring ≥2 hours after the loading dose of study drug or as urgent target vessel revascularization (any PCI or CABG) performed in response to ischemic symptoms involving the epicardial coronary artery that was the target vessel for the index procedure. Patients who did not undergo repeated coronary angiography after the initial procedure could not be determined to have CTVT. Major safety and efficacy end points were adjudicated by an independent clinical events committee that was blinded to treatment assignment.

The definition of MI, adapted from the standard American College of Cardiology/American Heart Association (ACC/AHA) definitions,[29,30] was dependent on pre-event biomarkers and the timing of the event. In all cases, if CK-MB was greater than the upper limit of normal (ULN) at the time of the suspected event, both an increase by ≥50% over the previous value and documentation that CK-MB was decreasing before the suspected recurrent MI were required. Within 24 hours after PCI, a subject would be considered to have had an MI with the ensuing CK-MB >3 times the ULN; within 24 hours of CABG, the threshold was CK-MB >10 times the ULN. Periprocedural MI could also be determined by either development of new, abnormal Q waves considered to be distinct from the evolution of an index MI or pathological findings of a new MI thought to be distinct from an MI in evolution before randomization. If the suspected MI was not associated with a procedure, the definition required CK-MB or cardiac troponin greater than ULN and either chest pain or ischemic discomfort lasting >20 minutes at rest or hemodynamic decompensation.

Statistical Considerations

All analyses were performed on an intent-to-treat basis of evaluable subjects. An evaluable subject was prespecified as a randomized subject who received at least the loading dose of study drug. Comparisons for the primary and secondary end points were between each prasugrel dosing group and clopidogrel using Fisher's exact test or the log-rank test. Other comparisons were done using χ^2 testing or ANOVA as appropriate. Major prespecified analyses included all prasugrel dosing groups combined versus clopidogrel and each prasugrel dosing group individually compared with clopidogrel. A sample size of 900 subjects was chosen to provide at least 80% power to detect a 2.5-fold increase in the risk of significant non–CABG-associated bleeding that was estimated from previous studies to occur in 5% to 7.5% of clopidogrel patients.[10,31] Secondary end points should be considered exploratory because the trial was not designed or powered to formally test these end points. Primary analyses were performed by an independent statistician at the contract research organization (Parexel, International) and verified by the sponsor and the TIMI Study Group independently. The TIMI Study Group had possession of and full access to all databases used for the analysis of the trial.

Results

Of the 905 patients randomized, 904 evaluable patients received at least 1 dose of study drug as follows: low-dose prasugrel, 199; intermediate-dose prasugrel, 200; high-dose prasugrel, 251; and clopidogrel, 254. A total of 848 patients (93.7%) completed the protocol; 53 (6%) discontinued for adverse events, personal decision, protocol violations, or physician decision; and 3 (0.3%) were lost to follow-up. There were no statistically significant differences in reasons for discontinuation from the trial among treatment groups.

Baseline and Procedural Characteristics

The baseline characteristics (Table 1) were balanced, with no significant differences between prasugrel- and clopidogrel-treated patients. Most patients (77%) were men; the median age was 60 years; and diabetes was frequent (27%). Unstable angina or NSTEMI was present in 40% of patients before PCI. Physician investigators elected to use GP IIb/IIIa inhibitors in 71% of patients.

As would be expected from the study design, nearly all patients underwent a PCI (99%), with 99% of patients who had PCI receiving at least 1 intracoronary stent. Multiple (≥2) stents were used in 35%. At least 1 drug-eluting stent was used in 54% of subjects. These procedural characteristics were well balanced among treatment groups.

Safety

In all groups combined, bleeding rates were low; 0.7% of patients experienced major bleeding, 1.1% experienced minor bleeding, and 2.4% experienced minimal bleeding. As would be expected in a trial of PCI, most of the bleeding episodes were related to instrumentation (68%), and the most frequent site of bleeding was the vascular access site. Most overall bleeding events (76%), including 4 of the 6 major hemorrhages, occurred during the index hospitalization. An intracranial hemorrhage (subdural hematoma) occurred in 1 patient (0.1%).

Major safety end points are summarized in Table 2. When examined by treatment group, there were low rates of major bleeding for all treatment groups (0.5% for prasugrel compared with 0.8% for clopidogrel). There was a higher incidence of but no statistically significant difference between the prasugrel groups individually or in combination compared with clopidogrel for the primary safety end point of the combination of TIMI major and minor non–CABG-related hemorrhage (1.7% versus 1.2%; hazard ratio [HR], 1.42; 95% CI, 0.40 to 5.08; Figure 2). Transfusion rates were low, with

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TABLE 1. Baseline Characteristics

	Prasugrel Dose, mg (Loading/Maintenance)				Clopidogrel Dose, mg (Loading/Maintenance)	
	40/7.5	60/10	60/15	All	300/75	*P*
No.	199	200	251	650	254	
Age <65 y, %	65	76	74	72	77	0.12
Age (median), y	60	59	59	59	58	0.10
BMI (median), kg/m^2	29.4	29.5	29.8	29.6	29.4	0.68
White, %	91	90	90	90	94	0.13
Female, %	24	25	21	23	23	0.92
Smoker, %	21	25	24	23	31	0.07
Diabetes mellitus, %	29	25	29	27	25	0.43
Prior aspirin, %	80	73	77	77	77	0.42
ST-segment depression, %	14	12	12	12	12	0.84
GP IIb/IIIa use, %	70	69	69	69	69	0.87
Mean TIMI risk score (SD)	2.4 (1.2)	2.2 (1.1)	2.4 (1.1)	2.3 (1.1)	2.4 (1.1)	0.46
TIMI risk score ≤2, %	50.3	63.0	54.2	55.7	49.6	0.18

BMI indicates body mass index. All characteristics are expressed as percents unless otherwise noted. Probability values are for the comparison of the combined prasugrel group vs clopidogrel.

0.9% of prasugrel-treated subjects and 1.1% of clopidogrel-treated patients receiving transfusion of at least 1 U of packed red blood cells. All treatment groups had significant hemorrhage rates lower than that expected from historical control subjects (5% to 7.5% major plus minor and 2% to 2.5% major).[10,31] There was, however, numerically more minimal bleeding in the high-dose prasugrel group (3.6%) compared with the low-dose (2.0%) and intermediate-dose (1.5%) groups and the clopidogrel group (2.4%). Although most bleeding events were in-hospital for all groups, the high-dose prasugrel group had numerically increased postdischarge minimal bleeding episodes (1.2%) compared with other prasugrel dosing groups (0.5% for each).

Efficacy

There was a lower incidence of but no statistically significant difference in MACE (Figure 3A) in the overall prasugrel group (7.2%) compared with the clopidogrel group (9.4%; $P=0.26$; HR, 0.76; 95% CI, 0.46 to 1.24).

Major efficacy end points are summarized in Table 2. The incidence of MI was numerically but nonsignificantly less frequent in the prasugrel group compared with the clopidogrel group (Table 2). When MI was analyzed by higher CK-MB cutoffs in a post hoc analysis, a trend toward greater reductions in larger infarctions occurred in the prasugrel group (Figure 4). Similarly, numerically lower rates of CTVT and recurrent ischemia were seen in prasugrel-treated patients (Table 2).

TABLE 2. Major Safety (Bleeding) and Efficacy End Points

Event	Prasugrel, n (%) (n=650)	Clopidogrel, n (%) (n=254)	*P**	HR (95% CI)
Bleeding				
Non-CABG TIMI major+minor	**11 (1.7)**	**3 (1.2)**	**0.590**	**1.42 (0.40–5.08)**
Non-CABG TIMI major	3 (0.5)	2 (0.8)	0.544	0.58 (0.10–3.46)
Non-CABG TIMI major+minor+minimal	27 (4.2)	9 (3.5)	0.685	1.17 (0.55–2.48)
Efficacy events				
MACE	**47 (7.2)**	**24 (9.4)**	**0.260**	**0.76 (0.46–1.24)**
Death	3 (0.5)	0	0.278	...
Stroke	3 (0.5)	0	0.278	...
MI	37 (5.7)	20 (7.9)	0.226	0.72 (0.42–1.24)
Recurrent ischemia	6 (0.9)	4 (1.6)	0.391	0.58 (0.16–2.05)
Severe ischemia	9 (1.7)	11 (3.5)	0.086	0.47 (0.2–1.14)
CTVT	4 (0.6)	6 (2.4)	0.024	0.26 (0.07–0.92)
Death/MI	40 (6.2)	20 (7.9)	0.349	0.78 (0.46–1.33)
Death/MI/CTVT	41 (6.3)	24 (9.4)	0.101	0.66 (0.40–1.10)

The trial primary end point was non–CABG-related TIMI major plus minor bleeding. Primary safety and efficacy end points are in bold. Recurrent ischemia required rehospitalization. Severe ischemia included patients for whom hospitalization was prolonged as a result of an ischemic episode. HR was not calculable for death and stroke because of zero cell in the clopidogrel group.

*Log-rank probability value.

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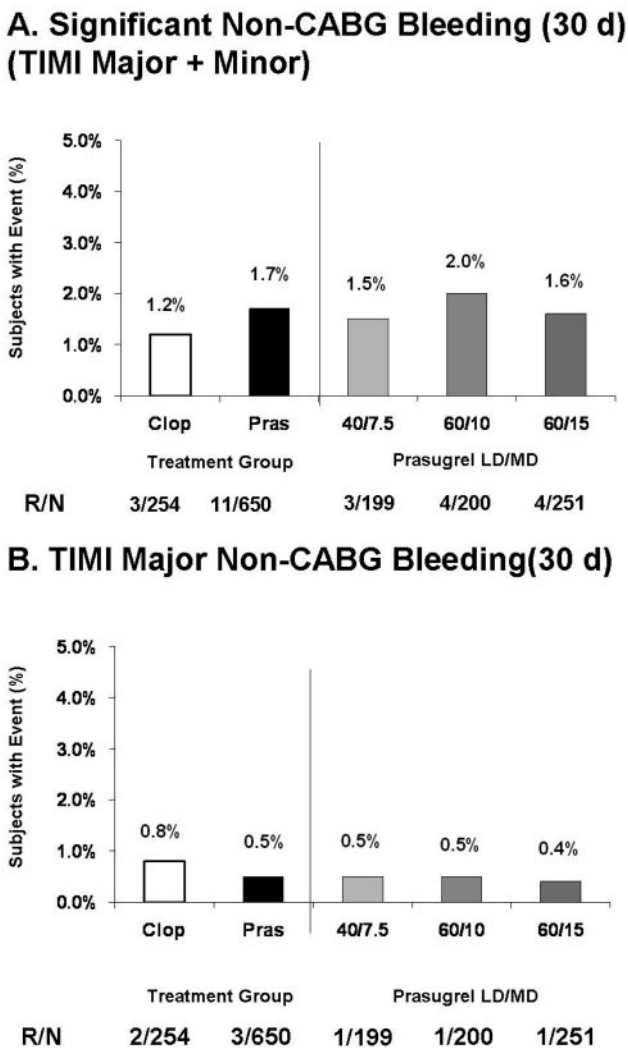

Figure 2. A, Significant bleeding. B, Major bleeding. Numbers above bar indicate percent of subjects experiencing event through 30 days of follow-up. Numbers below bars indicate number of subjects experiencing event/number at risk (R/N). LD/MD indicates loading dose/maintenance dose; 40/7.5, prasugrel 40-mg loading dose, 7.5-mg maintenance dose; 60/10, prasugrel 60-mg loading dose, 10-mg maintenance dose; 60/15, prasugrel 60-mg loading dose, 15-mg maintenance dose; Pras, all patients randomized to prasugrel; and clop, all patients randomized to clopidogrel.

Three deaths were observed in the high-dose prasugrel group (1.2%), whereas no deaths were seen in the other treatment arms. One patient was randomized, received only a loading dose, and died of complications from an elective coronary artery bypass surgery (sepsis). A second patient had a witnessed sudden death while exercising; an autopsy showed no evidence of stent thrombosis or new ischemic event. The third death was not witnessed, and no autopsy was performed. There was no statistically significant difference in death among the prasugrel groups or between all prasugrel groups and the clopidogrel group (Table 2).

Two strokes were observed in the intermediate-dose prasugrel group (1.0%) and were nonhemorrhagic. One stroke was seen in the high-dose prasugrel group (0.4%) and was judged to be hemorrhagic. This patient had a CT scan showing a small subdural hematoma. There were no episodes of intraparenchymal or epidural hemorrhage. There was no statistically significant difference in this end point among the prasugrel groups or between the combined prasugrel group and the clopidogrel group (Table 2).

Subgroups

Separate analyses were performed on the basis of the use of GP IIb/IIIa inhibitor, gender, age, smoking status, prior aspirin use, urgent versus elective PCI, and indication for PCI. There were no significant interactions between subgroup and treatment effect.

Discussion

This is the first report of the use of a novel thienopyridine antiplatelet agent, prasugrel (CS-747, LY640315), in patients undergoing elective or urgent PCI. This trial was designed to evaluate ranges of both loading and maintenance doses of prasugrel compared with standard therapy with clopidogrel. Bleeding rates for all treatment groups were lower than expected for clopidogrel plus aspirin from prior PCI trials.[10,17,31] There was a suggestion of an increase in TIMI minimal bleeding in the postdischarge period with the highest dose of prasugrel compared with all other treatment arms. This suggests a clinically meaningful dose-response relationship with this compound.

This trial was designed as a phase 2 safety study. The primary goal was to assess the bleeding risk associated with prasugrel and the feasibility of a phase 3 trial. It was not designed or powered to detect clinical efficacy. Therefore, with 904 subjects in 4 treatment arms (including an active comparator), the study did not have statistical power to detect clinically meaningful differences in efficacy end points. Accordingly, efficacy results should be interpreted with caution. Point estimates for selected ischemic end points were lower in the prasugrel-treated patients. However, except for CTVT, these events failed to meet statistical significance and formally should not be considered evidence of being different.

In aggregate, these data showed that treatment with prasugrel resulted in acceptable levels of bleeding with contemporary PCI practices; there were low rates of major bleeding, significant (major plus minor) bleeding, and transfusions. There were nonsignificantly higher rates of minor and minimal bleeding in patients treated with prasugrel, especially at the highest dose studied. In contrast, there were nonsignificantly lower rates of ischemic events after PCI when patients were treated with prasugrel compared with clopidogrel. This combination of features warrants further study.

If a similar magnitude of reduction in efficacy end points seen in this trial can be corroborated in a larger trial powered to detect clinical efficacy differences with acceptable safety, this would constitute an improvement over the current standard of care. Although the present trial was not designed to assess mechanisms of action, multiple features of prasugrel could explain these putative differences, including increased level of platelet inhibition,[26] and/or diminished interpatient

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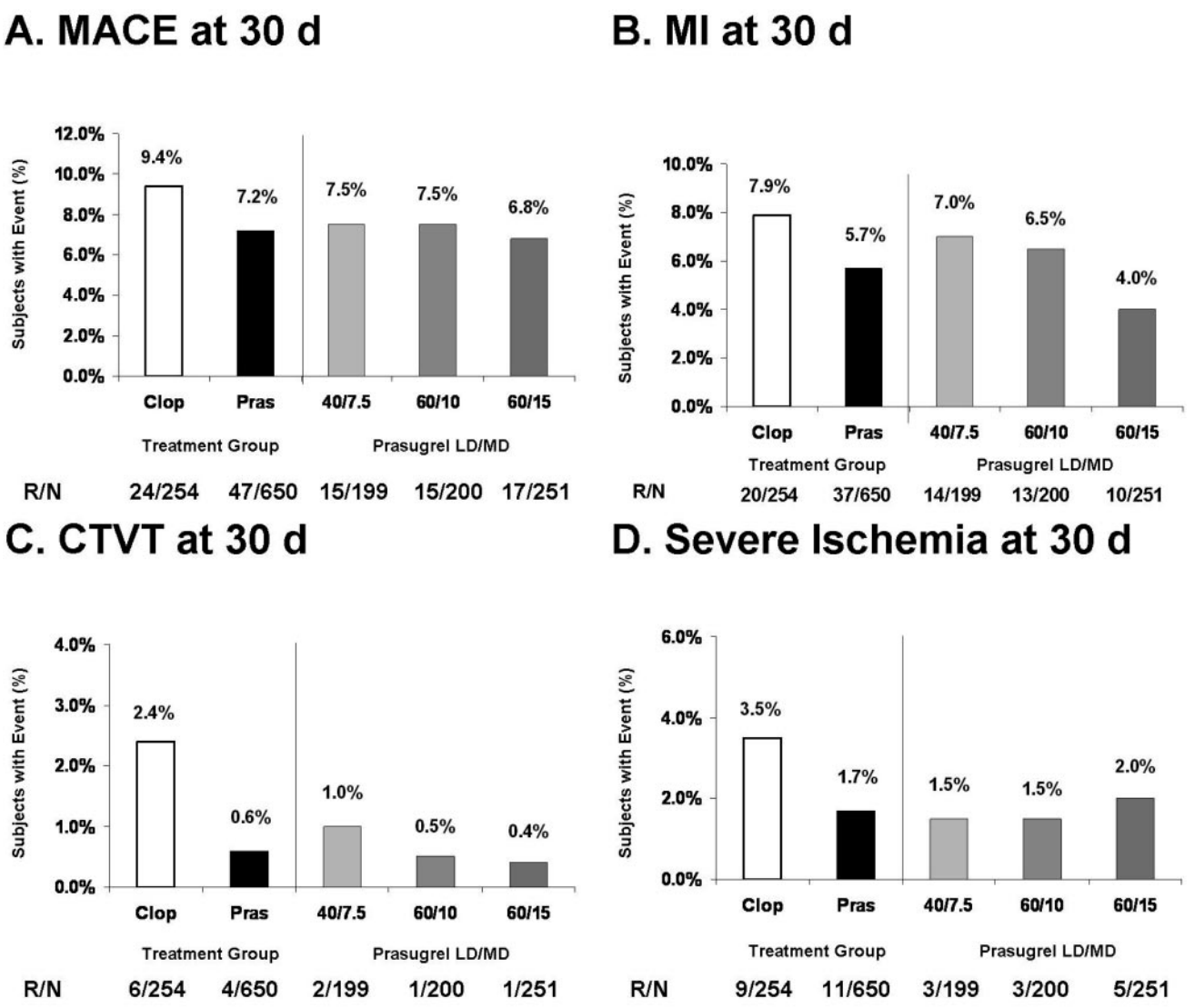

Figure 3. Major efficacy end points through 30 days. A, MACE. B, MI. C, CTVT. D, Severe ischemia (requiring rehospitalization or prolonging ongoing hospitalization). Numbers above bar indicate percent of subjects experiencing event through 30 days of follow-up. Numbers below bars indicate number of subjects experiencing event/number at risk (R/N). Abbreviations as in Figure 2.

variability of antiplatelet effect compared with standard clopidogrel therapy.[25]

Study Limitations

The trial was designed as a safety trial with a primary end point comparing bleeding rates. Bleeding rates in the control arm were lower than expected, resulting in reduced power for the primary safety end point. Although the rates of bleeding were also low in the prasugrel-treated patients, one cannot exclude a moderate increase in bleeding with prasugrel. The trial was not intended to be powered to specifically examine efficacy end points. As a result, the CIs around the estimates of ischemic event reductions are wide, and the magnitude of the decrease in event rates should be interpreted with caution. However, the biological plausibility of the enhanced antiplatelet effect and the appearance of a dose-response relationship with prasugrel provide support that these observations could be clinically meaningful. To the best of our knowledge, no adequately powered study has compared a 300-mg loading dose with higher loading doses of clopidogrel or clopidogrel pretreatment with administration of loading doses of clopidogrel during PCI with clinical end points, but some operators have adopted these practices on the basis of mechanistic information. The design of JUMBO–TIMI 26 does not allow for the assessment of prasugrel compared with higher doses of clopidogrel or the effects of longer durations of study drug pretreatment. Information about the safety of prasugrel in populations excluded from this trial (including the elderly or patients undergoing primary PCI for STEMI) cannot be determined from this trial and need to be clarified in future studies.

Conclusions

Thienopyridine antiplatelet agents are an important component of adjunctive therapy for PCI. Prasugrel is a novel, thienopyridine $P2Y_{12}$ antagonist that can achieve more rapid

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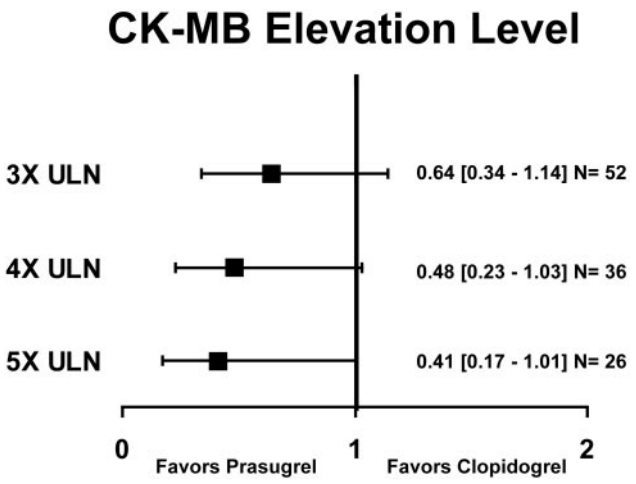

Figure 4. Hazard ratio and CIs for MI at 30 days using increasingly stringent CK-MB cutoffs. The notations 3×, 4×, and 5× indicate 3, 4, or 5 times ULN CK-MB. Number in parentheses notes number of MIs meeting this definition.

onset and higher levels of inhibition of platelet aggregation. In this study, designed to assess safety, prasugrel and clopidogrel, when administered at the time of PCI, resulted in low rates of bleeding, although modest increases associated with prasugrel cannot be excluded given the low power of the study resulting from lower-than-expected bleeding rates in both treatment groups. The results of this trial serve as a foundation for a large phase 3 clinical trial, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON)-TIMI 38, designed to assess both efficacy and safety.

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Disclosure

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